Amendments to the Drawings:

The attached sheet of drawings includes changes to Figure 1. This sheet replaces original Figure 1.

Attachment: Replacement Sheet (Figure 1).

REMARKS

Reconsideration of the present application in view of the above amendments and the following remarks is respectfully requested.

Claims 1-21 and 23-25 are pending, of which claims 16-21 are withdrawn from consideration as directed to a non-elected invention. Claims 1, 6 and 16 have been amended to clarify the claimed subject matter and without prejudice to future prosecution of the previously pending claims or acquiescing to the rejections in the Office Action. Support for the amendments to claims 1 and 16 may be found, for example, at lines 1-7 of the second paragraph on page 6 of the present application. Support for the amendments to claim 6 may be found, for example, in the paragraph bridging pages 6 and 7. No new matter has been added.

Election/Restriction

As discussed in detail below, the use of a nucleic acid binding solid phase in a liquid phase that comprises NH_4^+ or NH_3 and a chaotrope with a pH ranging from 8.5 to 9.5 for nucleic acid isolation recited in both method claims (*i.e.*, claims 1-15 and 23-25) and kit claims (*i.e.*, claims 16-21) is novel and inventive. Applicants submit that this novel and inventive feature links the method and kit claims of the present application together. Accordingly, Applicants respectfully request that the restriction between Groups I and II be withdrawn.

Drawings

Applicants thank the Examiner for noting the informality in Figure 1 with respect to an inconsistency between the graph and the figure keys. Applicants submit replacement Figure 1 that deletes the "50 µl blood" text from the graph. Accordingly, Applicants respectfully request that this objection to Figure 1 be withdrawn.

Claim Rejections Under 35 U.S.C. 112, Second Paragraph

Claim 6 stands rejected under 35 U.S.C. 112, second paragraph, as indefinite. More specifically, it is noted in the Office Action that the language "the NH_4^+ or NH_3" does not have sufficient antecedent basis. Applicants have amended both claims 1 and 6 so that the

language in amended claim 6 has support in amended claim 1. Accordingly, Applicants respectfully request that this rejection be withdrawn.

Claim Rejections Under 35 U.S.C. 102

Claims 1-5, 7, 8, 11-13 and 15 stand rejected under 35 U.S.C. 102(b) as anticipated by Sauer *et al.* (WO 99/61603, "Sauer").

To facilitate allowance, Applicants have amended claim 1 to clarify that contacting a nucleic acid-containing sample with a nucleic acid binding solid phase is performed in the presence of a liquid phase that comprises a chaotrope and NH_4^+ or NH_3 (as opposite to the source of NH_4^+ or NH_3). Applicants submit that because Sauer does not disclose step (d) of amended claim 1, it does not anticipate the subject matter currently claimed in the present application.

Applicants disagree with the assertion in the Office Action about step (c) of claim 1 (*see*, first paragraph on page 5). More specifically, Applicants disagree that Sauer, in the first paragraph on page 7, teaches adjusting pH using amino acids. That section only discloses **ω-amino acids** as alkaline reacting substances for adjusting pH, rather than amino acids in general.

In view of the disclosure of **ω-amino acids** rather than amino acids in general in Sauer, to anticipate the subject matter currently claimed in the present application, this reference has to additionally disclose that (1) amino acid deaminases are present in a solution that comprises a chaotrope and ω-amino acids, (2) amino acid deaminases are capable of producing NH_4^+ or NH_3 from **ω**-amino acids, (3) amino acid deaminases produce NH_4^+ or NH_3 from omega amino acids even in the presence of a chaotrope. As discussed in detail below, Sauer does not disclose all the above-noted features and thus does not anticipate the subject matter currently claimed in the present application.

First, Sauer is **silent** with respect to amino acid deaminases. Thus, there has to be implicit or inherent disclosure of amino acid deaminases in Sauer for this reference to anticipate the claimed subject matter of the present application. Should this ground of rejection be maintained, Applicants respectfully request that the implicit or inherent disclosure of amino acid deaminases in Sauer be articulated in the next Office Action. In this regard, Applicants note that "[t]o establish inherency, the extrinsic evidence 'must make clear that the missing descriptive

matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.' " *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999) (citations omitted).

Second, even assuming for the sake of argument that Sauer implicitly or inherently discloses amino acid deaminases, there is no evidence showing that amino acid deaminases are capable of making NH_4^+ or NH_3 using **ω**-amino acids as substrates. Because all of the 20 amino acids commonly found in proteins are α amino acids (*i.e.*, the carboxyl and amino groups of the amino acids bind to the same carbon atom), it would be reasonable to speculate that the substrates of deaminases are likely to be common, naturally occurring amino acids (*i.e.*, α amino acids), rather than **ω**-amino acids. Accordingly, should this ground of rejection be maintained, Applicants respectfully request that evidence be presented to show that there exist deaminases that are capable of making NH_4^+ or NH_3 from **ω**-amino acids.

Third, even assuming for the sake of argument that Sauer implicitly or inherently discloses amino acid deaminases that are capable of making NH_4^+ or NH_3 from **ω**-amino acids, the deaminases would likely be **inactivated** by the chaotrope that is also present in the solution that contains ω-amino acids. Sauer provides that chaotropic substances are known to alter the secondary structure of polymers in general (*see*, page 9, the second and third to the last lines), such as 2 to 4 M solutions of guanidinium hydrochloride or guanidinium thiocyanate (*see*, page 10, first paragraph, lines 5 to 7). Most proteins, if not all proteins, would be denatured and inactivated under such conditions.

In view of the above remarks, Applicants submit that this ground of rejection under 35 U.S.C. 102(b) has been overcome. Applicants respectfully request that this rejection be withdrawn.

Claim Rejections Under 35 U.S.C. 103(a)

Claims 1-9, 12-15 and 23 stand rejected under 35 U.S.C. 103(a) as unpatentable over McKernan (US 2002/0106686, "McKernan") in view of Rauth et al. (WO 01/19980, "Rauth") as evidenced by Horne et al. (Analyst 124: 87-90, 1999) and by Alleman (Free

Ammonia-Nitrogen Calculator & Information [online], 1998). More specifically, it is asserted in the Office Action that (1) McKernan relates to nucleic acid isolation by binding nucleic acids to a solid phase in the presence of a chaotropic salt and PEG and teaches every limitation recited in claim 1 except providing a source of NH_4^+ or NH_3, (2) Rauth also relates to nucleic acid isolation by binding nucleic acids to a solid phase in the presence of a chaotropic salt and PEG and lists ammonium chloride as an alternative salt, and (3) Horne teaches that although weak, chloride is still a chaotrope. It is further asserted that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute ammonium chloride for the chloride salts listed by McKernan when practicing his method because Rauth teaches a similar method and also teaches ammonium chloride as an art recognized equivalent of chloride salts taught by McKernan for the purpose of enhancing binding of nucleic acids to a solid phase carrier in the presence of PEG. It is also asserted that combining McKernan and Rauth would have arrived at the claimed methods because ammonium chloride would provide a source of ammonium and a chaotrope (chloride).

Applicants respectfully traverse this ground of rejection. The subject matter currently claimed in the present invention is a method for isolating nucleic acid from a nucleic acid-containing sample via a nucleic acid binding solid phase in the presence of a liquid phase that comprises chaotrope and NH_4^+ or NH_3 and has a pH in the range of 8.5 to 9.5. The present inventors have found that the **combination** of (1) the presence of NH_4^+ or NH_3 in the liquid phase and (2) a pH in the range of 8.5. to 9.5 of the liquid phase increases the isolated nucleic acid yield (*see*, the paragraph bridging pages 3 and 4 of WO 03/084976). Such an increase in the isolated nucleic acid yield is greater than that when a nucleic acid binding solid phase is used (1) in a liquid phase that comprises NH_4^+ or NH_3 but with a pH other than in the range of 8.5 to 9.5, or (2) in a liquid phase that does not comprise NH_4^+ or NH_3 but has a pH in the range of 8.5 to 9.5. In fact, the simple increase of pH to 8.5 in the absence of NH_4^+ or NH_3 does not affect the yield of the isolated nucleic acid. However, the pH of the liquid phase in the presence of NH_4^+ or NH_3 does have an effect on the increased yield of the isolated nucleic acid. Thus, to maximize the isolated nucleic acid yield, both the presence of NH_4^+ or NH_3 in a liquid phase in which a nucleic acid binding solid phase contacts a nucleic acid-containing sample and the pH range of 8.5 to 9.5 of the liquid phase are required.

McKernan relates to methods and reagents for isolating nucleic acids. In pertinent parts, the methods comprise contacting a nucleic acid sample with a solid phase carrier in the presence of a DNA precipitating agent and optionally a salt. The nucleic acid sample may be cells, lysates prepared from cells, nucleic acid samples eluted from agarose and polyacrylamid gels, *etc.* (paragraph [0077]). The solid phase carrier is able to reversibly bind to nucleic acids in the sample and include various microparticles such as carboxyl-coated or amine-coated paramagnetic microparticules, particles, fibers, beads, *etc.* (paragraphs [0012] and [0062]-[0064]). The nucleic acid precipitating agent is a composition that causes a nucleic acid molecule to go out of solution and may be an alcohol such as a short chain alcohol and a polyalkylene glycol (paragraph [0010]). Examples of useful polyalkylene glycols include polyethylene glycol (PEG) having various molecular weights and polypropylene glycol (paragraphs [0010] and [0058]). The salt is to facilitate the adsorption of the nucleic acid to the solid phase carrier (paragraph [0060]). Suitable salts include sodium chloride, lithium chloride, barium chloride, potassium chloride, calcium chloride, magnesium chloride and cesium chloride. McKernan further provides that, in general, the presence of salt functions to minimize the negative charge repulsion of the nucleic acid molecules and that many other salts can also be used. The pH of the composition that comprises a solid phase carrier, a nucleic acid precipitating agent and optionally a salt can be formulated as to adjust the electronegativity of the solid phase carrier, *e.g.*, the functional group coating the surface of the solid phase carrier, and therefore alter the binding affinity of the solid phase carrier for nucleic acids (paragraphs [0013] and [0014]). Depending on the desired electronegativity of the solid phase carrier, the pH may be formulated in the range of 2.0-11.0.

Applicants submit that one of ordinary skill in the art would not have modified McKernan to arrive at the presently claimed subject matter. From McKernan to arrive at the presently claimed invention, such a person has to modify McKernan by (1) selecting the combination of a specific salt and a specific pH range as the factor to modify, (2) selecting an ammonium salt among many other salts, and (3) choosing the pH to be in the range of 8.5 to 9.5 from a broader range of 2.0 to 11.0. As discussed in more detail below, no reasons have been provided in McKernan or the other cited references for a skilled artisan to do so. Without such reasons, the probability that one of ordinary skill in the art happens to arrive at the presently

claimed invention is very low. As such, such a person would not have modified McKernan to arrive at the subject matter currently claimed in the present application.

First, the probability for one of ordinary skill in the art to choose the combination of a specific salt and a specific pH range is low. More specifically, at least five factors are discussed in McKernan that relate to the isolation of nucleic acids: (1) DNA samples (paragraph [0077]), (2) solid phase carriers (paragraphs [0012] and [0062]-[0064]), (3) nucleic acid precipitating agents (paragraphs [0010] and [0058]), (4) salts (paragraph [0011]), and (5) pH (paragraphs [0013] and [0014]). Among these five factors, no reason is provided by McKernan and the other cited references for one skilled in the art to combine a specific salt with a specific pH range for the liquid phase in which a nucleic acid binding solid phase and a nucleic acid sample contact each other. Without such a suggestion, the probability for one skilled in the art to choose the combination of the salt and the pH is one out of thirty-one (1/31).

Second, the probability for one of ordinary skill in the art to choose an ammonium salt in combination with a specific pH range is also low. McKernan discloses six exemplary salts, but does not specifically disclose any ammonium salts. Rauth discloses, in addition to the six exemplary salts, six additional salts including ammonium chloride. In addition, McKernan provides that many other salts can also be used. None of the cited references indicates that an ammonium salt is preferred. Thus, without such an indication, the probability for one of ordinary skill in the art to choose an ammonium salt is at most one out of twelve (1/12), and may be much less taking the many other salt forms that are generally but not specifically disclosed in McKernan.

Third, the probability for one of ordinary skill in the art to choose the pH range of 8.5 to 9.5 is also low. The pH range disclosed in McKernan is between 2.0 and 11.0, whereas Rauth is silent with respect to the pH at which a nucleic acid binding solid phase is in contact with a nucleic acid sample. Thus, without any indication that the pH range of 8.5 to 9.5 is preferred, the probability for one of ordinary skill in the art to choose a pH range of 8.5 to 9.5 is one out of nine (1/9).

In view of the low probabilities for one of ordinary skill in the art to combine a specific salt with a specific pH range and further choose an ammonium salt as the specific salt and a range of 8.5 to 9.5 as the specific pH range, the overall probability for such a person to

modify McKernan to arrive at the subject matter currently claimed in the present application is very low, that is, at most 1/3348, and may be much less taking the many other salt forms that are generally but not specifically disclosed in McKernan. As such, such a person would not have modified McKernan to arrive at the subject matter currently claimed in the present application.

Applicants disagree with the characterization of the modification from McKernan to the subject matter recited in claim 1 of the present application in the Office Action as merely a substitution of a salt in McKernan with ammonium chloride, an equivalent salt, disclosed in Rauth. Such a characterization disregards the presence of multiple factors that affect nucleic acid isolation according to McKernan, the significance of recognizing the combination of a specific salt and a specific pH range as critical to the yield of isolated nucleic acids, and the selection of a specific pH range in combination of substituting a salt in McKernan with ammonium chloride.

Applicants further submit that the present application is distinguishable from *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348 (Fed. Cir. 2007). First, in *Pfizer*, it was known in the art that the salt form of the compound at issue would affect its properties and was a critical factor to experiment with. To the contrary, without knowing the advantage associated with contacting a nucleic acid sample with a nucleic acid binding solid phase in the presence of ammonia or ammonium **and** in the specific pH range of 8.5 to 9.5 as disclosed in the present application, one of ordinary skill in the art would not have recognized the combination of ammonia or ammonium and the specific pH range of 8.5 to 9.5 as a critical factor in improving the yield of isolated nucleic acids, and thus would not have arrived at the claimed subject matter of the present application. In this regard, Applicants note that a particular parameter must first be recognized as a result-effective variable, *i.e.*, a variable which achieves a recognized result, before the determination of the optimum or workable ranges of said variable might be characterized as routine experimentation. *In re Antonie*, 559 F.2d 618 (CCPA 1977) (The claimed wastewater treatment device had a tank volume to contractor area of 0.12 gal./sq. ft. The prior art did not recognize that treatment capacity is a function of the tank volume to contractor ratio, and therefore the parameter optimized was not recognized in the art to be a result-effective variable) (*see*, MPEP 2144.05 II.B. at page 2100-152, eighth edition). Second, in *Pfizer*, the possible alternatives were 53 alternatives. To the contrary, as discussed above, the possible alternative is

at least 3348 in the present application. Applicants disagree with the assertion in the Office Action that "the number of possible alternatives taught by Rauth (Rb, Fr, Be, Sr, Ra and NH_4) was even smaller than the 53 alternatives in *Pfizer*." Rauth specifically discloses 12 chloride salt forms. The six listed in the Office Action only include those not disclosed in McKernan. To select an ammonium salt as the salt form, one of ordinary skill in the art has to at least choose one out of 12 salts disclosed in McKernan and Rauth. In addition, McKernan provides that many more salts forms may be used. Thus, the possibility of selecting an ammonium salt may be much less than 1/12. Moreover, such an assertion in the Office Action disregards, in addition to selecting the combination of a specific salt form and a specific pH range as a critical factor to modify, the selection of the specific pH range of 8.5 to 9.5 in combination with an ammonium salt.

In view of the above remarks, Applicants submit that this ground of rejection under 35 U.S.C. 103 has been overcome. Applicants respectfully request that this rejection be withdrawn.

Claims 10, 24 and 25 stand rejected under 35 U.S.C. 103(a) as unpatentable over McKernan (US 2002/0106686, "McKernan") in view of Rauth et al. (WO 01/19980, "Rauth") as evidenced by Horne et al. (Analyst 124: 87-90, 1999) and by Alleman (Free Ammonia-Nitrogen Calculator & Information [online], 1998) and further in view of Laugharn et al. (US 6,111,096).

Applicants respectfully traverse this ground of rejection. As discussed above, McKernan, Rauth, Horne and Alleman, either alone or in combination, without recognizing the advantage associated with the use of ammonium or ammonia at a pH range of 8.5 to 9.5, fail to provide reasons for one of ordinary skill in the art to modify McKernan to arrive at the subject matter claimed in the present application. In addition, also as discussed above, without such reasons, the probability that one of ordinary skill in the art happens to arrive at the presently claimed invention is very low. Because Laugharn does not provide such reasons or otherwise increase the probability for one of ordinary skill in the art to arrive at the presently claimed invention, Applicants submit that the rejected claims have not been rendered obvious by the cited references, either alone or in combination.

In view of the above remarks, Applicants submit that this ground of rejection under 35 U.S.C. 103 has been overcome. Applicants respectfully request that this rejection be withdrawn.

Applicants believe that the remaining claims of the present application are now allowable. Favorable consideration and a Notice of Allowance are earnestly solicited.

The Director is hereby authorized to charge any additional fees due by way of this Amendment, or credit any overpayment, to our Deposit Account No. 19-1090.

Respectfully submitted,

SEED Intellectual Property Law Group PLLC

/Qing Lin/

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Enclosure:
Replacement Figure 1

QXL:kw

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